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IN THIS ISSUE

Focus of the Month:
Alcohol Use Disorder

Learning Objectives
After reading these articles, you should be able to:

1. Identify effective pharmocological treatments for alcohol use disorder (AUD).
2. Determine best practices for treating AUD and its associated comorbid conditions.
3. Summarize some of the findings in the literature regarding addiction treatment.

Medications for Alcohol Use Disorder: An Overview

Special Double Issue! Worth 2 CME credits!

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Ms. Warshaw has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

Highlights From This Issue

- Many medications have shown efficacy in treating alcohol use disorder (AUD), though some have better evidence.
- AUD can be a challenge to treat in patients with psychiatric comorbidities, but evidence suggests that standard approaches work.
- A lot can be learned from liver function tests if you know what to look for.
- Co-locating contraceptive services and opioid use disorder treatment decreases rates of unintended pregnancy and is cost effective.

Alcohol use disorder (AUD) is the most common substance use disorder by far, with a lifetime prevalence of nearly 30%. It is also vastly undertreated; less than 20% of people with AUD ever receive treatment (Grant BF et al, *JAMA Psychiatry* 2015;72(8):757–766). To make matters worse, there are only three FDA-approved medications for AUD: disulfiram, acamprosate, and naltrexone. However, there are quite a few other medications being used off label to treat AUD. We'll walk you through the options, the current evidence, and some ways of choosing between the available medications.

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Q&A With the Expert

Real-World Alcohol Use Disorder Treatment

Ismene Petrakis, MD

Addiction psychiatrist and professor at Yale School of Medicine. Chief of Mental Health, VA Connecticut Healthcare System, New Haven, CT.

Dr. Petrakis has disclosed that she participated in a study in which she did not receive any compensation from Alkermes apart from medication and Alkermes did not fund the study. Dr. Capurso has reviewed this material and found no evidence of bias pertaining to this educational activity.

CATR: Please tell us about yourself.
Dr. Petrakis: I'm an addiction psychiatrist, professor at Yale School of Medicine, and the Chief of Mental Health for the VA Connecticut Healthcare System. I have several research focuses, one of which is the treatment of individuals with comorbid psychiatric illness and alcohol use disorder (AUD).
CATR: We know AUD prevalence is higher among patients with mental illness. But how big of a problem is it really?
Dr. Petrakis: It's a big problem. The prevalence of AUD in people who have mental illness is significantly higher than it is in the general population. And the risk goes both ways. By that I mean, if you start with a group of patients with psychiatric illness, the prevalence of AUD is higher than

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Expert Interview – Real-World Alcohol Use Disorder Treatment

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the general population, and if you start with a group of patients with AUD, the prevalence of psychiatric illness will be elevated. This holds for inpatient units and outpatient facilities alike, which suggests that AUD is important to look for in any mental health treatment setting, not just a specialty addiction clinic.

CATR: And how does the prevalence of AUD break down by diagnosis?

Dr. Petrakis: That's a tough question to answer exactly because, believe it or not, there is no comprehensive single study that answers this question. So, that means comparing studies with differing methodologies. But it's clear that there are increases across the board, with bipolar disorder probably conferring the greatest risk. For some context, the 12-month prevalence of AUD in the general population is less than 10% (Hasin DS and Grant BF, *Soc Psych Psychiatr Epidemiol* 2015;50(11):1609–1640). That number is in the range of 20% for schizophrenia; 30% for depression, ADHD, anxiety disorders, and PTSD; and up to 40% for bipolar disorder (Castillo-Carniglia A et al, *Lancet Psychiatry* 2019;6(12):1068–1080).

CATR: How do you suggest clinicians make a diagnosis? What should they be looking for specifically?

Dr. Petrakis: The first step is to make sure that there is a protocol for screening in place. Every patient having an intake in a mental health setting should be screened for AUD, and that screening should be repeated periodically, say every year or so. Here at the VA, we use the AUDIT-C, which is pretty easy to use *(Editor's note: See AUDIT-C questionnaire on page 4).* Whatever screening tool you use, be sure you know what it's meant for; the AUDIT-C won't diagnose AUD, but it can identify who needs further investigation (Bush K et al, *Arch Intern Med* 1998;158(16):1789–1795; www.tinyurl.com/mba74m3f).

CATR: By "needs further investigation," are you referring to identifying patients with risky or hazardous drinking as opposed to necessarily meeting DSM-5 criteria for AUD?

Dr. Petrakis: Correct. The DSM-5 definition does not define quantity or frequency; what's specifically important in making an AUD diagnosis is pattern of use. The DSM emphasizes use despite negative consequences, whether those consequences are social, psychological, or medical. People with AUD continue to drink despite their alcohol use causing problems. On the other hand, there are amounts of alcohol associated with medical problems, and consuming above this limit is what we call risky drinking, or hazardous drinking. Sometimes, patients consuming alcohol in the hazardous range aren't facing any negative consequence yet and therefore don't meet criteria for AUD, though they are certainly at a higher risk for AUD and medical issues down the line. These patients might be amenable to just some education. It can go a long way just telling them, "If you're drinking above a certain amount, you are at risk of having alcohol-related problems."

CATR: And what is that amount?

Dr. Petrakis: It's different for men and women. For men, it's greater than four standard drinks in a sitting or more than 14 drinks in a week. For women, it's greater than three standard drinks in a sitting or more than seven drinks in a week. There are preliminary data that even small amounts of alcohol can be detrimental to health (Topiwala A et al, *medRxiv* 2021. Epub ahead of print), causing some to recommend that these guidelines be revised downwards, so these numbers may change.

CATR: That's quite a difference between men and women.

Dr. Petrakis: Women's higher total body fat percentage and slower ability to metabolize alcohol is part of the reason. But also, it is thought that there is a telescoping effect, or accelerated progression of disease, where women tend to get medical problems more quickly than men (Diehl A et al, *Eur Arch Psychiatry Clin Neurosci* 2007;257(6):344–351). It's not clear why that is.

CATR: And these are standard drinks you are referring to, correct?

Dr. Petrakis: Yes. A standard drink is 14 grams of alcohol, which is a regular beer, a glass of wine, a mixed drink—they are all about equivalent. But many drinks have higher alcohol content than what is considered typical. High-alcohol beers and wines and high-proof liquors are common these days. And

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some containers hold more than you might think. Those red Solo cups are very bad—you can pour a lot in there! In order to really understand a patient's drinking pattern, you have to ask what exactly the patient is drinking and convert it to standard drinks. It's helpful to have a working knowledge of basic terms, too, like how many drinks are in a fifth, a nip, a half-pint, etc. *(Editor's note: See "Common Terms for Alcohol Drink Sizes" table on page 4.)*

CATR: Let's talk about medications for AUD. How generalizable are the findings of research trials for these medications to patients with mental illness?

Dr. Petrakis: That's a good question. A lot of studies, especially the ones that led to FDA approval, excluded people who had co-morbid psychiatric disorders. But there is growing interest in looking at these medications for patients with comorbidities, especially those that commonly co-occur with AUD, like depression, anxiety, and maybe PTSD.

CATR: Can you talk a little bit about specific medications?

Dr. Petrakis: Sure. There are three FDA-approved medications for AUD: disulfiram, naltrexone, and acamprosate. Disulfiram might be a special case, but naltrexone and acamprosate are certainly safe and effective in patients with comorbid psychiatric illness.

CATR: Why is disulfiram a special case?

Dr. Petrakis: Well, disulfiram can cause psychosis. It's thought to occur because disulfiram inhibits dopamine beta-hydroxylase, an enzyme that breaks down dopamine and norepinephrine. Reports show that this is dose dependent, and psychosis tends to occur in people who've received high doses (Mohapatra S and Rath NR, *Clin Psychopharmacol Neurosci* 2017;15(1):68–69). So, it's generally safe to use at typical doses of 250–500 mg.

CATR: Can disulfiram be used for patients with preexisting psychotic disorders?

Dr. Petrakis: It's not contraindicated, though I'd recommend using the lowest effective dose and monitoring carefully.

CATR: What about naltrexone and its effect on the endogenous opioid system?

Dr. Petrakis: As an opioid antagonist, people have wondered about naltrexone's ability to precipitate or worsen depression and perhaps cause anhedonia. Mechanistically this possibility makes sense, but there's no evidence that it occurs at all. If it does, it's very uncommon. Of course, as an opioid blocker, naltrexone is contraindicated for patients taking opioid analgesics. But keep it in mind for people with comorbid opioid use disorder (OUD) because the intramuscular form is FDA approved to treat both.

CATR: And acamprosate?

Dr. Petrakis: It's pretty benign and very well tolerated.

CATR: It doesn't have great efficacy data.

Dr. Petrakis: That's partially true. Some early data were promising, especially in trials out of Europe, and there have been studies here and there showing that it's effective. But large trials in the US have been mixed. The largest one was the COMBINE trial, which was negative (Anton RF et al, *JAMA* 2006;295(17):2003–2017). Another trial around the same time showed a little bit of a signal, but again it wasn't super encouraging (Mason BJ et al, *J Psychiatric Res* 2006;40(5):383–393).

"In general, you shouldn't wait to treat an AUD comorbid issue. The old-fashioned approach said patients should be sober for a month before treating depression because mood gets better over time. While this can be true, you can then have patients waiting around suffering from depression, risking dropping out of treatment, and possibly having a bad outcome."

Ismene Petrakis, MD

CATR: Other non-FDA-approved medications are used for AUD as well. How do you approach choosing between them all?

Dr. Petrakis: For me, unless there is a contraindication, I think the first line is naltrexone. It's FDA approved and has more evidence than anything else. It's well tolerated and can help with cravings. The other FDA-approved medications, acamprosate and disulfiram, can be considered second line, though it's very dependent on the clinical circumstances, especially when it comes to disulfiram. There are a lot of practitioners who shy away from disulfiram, and I understand that. I think it's a good medication, but I wouldn't use it in patients with very poor impulse control or significant medical illness that could put them at risk if they have a disulfiram-alcohol reaction. Adherence is also a big issue with disulfiram; as somebody taught me when I was a resident, it doesn't help with sobriety if it's sitting in a dresser drawer. It's most useful if the patient is observed taking it.

CATR: And the non-FDA-approved medications?

Dr. Petrakis: I would go to those if naltrexone and acamprosate aren't working, and maybe disulfiram if the patient is an appropriate candidate for that medication. There are a few medications that have been tested a lot but don't have FDA approval. The first option in my mind is topiramate. There's a lot of evidence for topiramate even though it's not approved (Guglielmo R et al, *CNS Drugs* 2015;29(5):383–395). The problem with topiramate is its side effect profile; it can cause people to feel cognitive slowing.

CATR: And gabapentin?

Dr. Petrakis: I'd probably go to gabapentin after topiramate. Clinically it's used all the time, and there's some evidence for it, though that evidence is a bit mixed (Kranzler HR et al, *Addiction* 2019;114(9):1547–1555). While it can be helpful for some patients, I'm a little cautious about gabapentin since it can cause cognitive impairment. It might have some sedating effects that might help with anxiety, but that comes with the downside of being sedating. There are reports of gabapentin being

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used recreationally, though personally I don't really see that much. A bigger concern is that gabapentin might amplify respiratory depression in patients who use opioids. In fact, it is associated with increased risk of opioid overdose (Gomes T et al, *PLoS Med* 2017;14(10):e1002396), so I would be very cautious in patients with comorbid AUD and OUD.

CATR: Any other medications?

Dr. Petrakis: Others have been studied, but nothing with strong support and nothing I would use routinely. *(Editor's note: See "Medications for Alcohol Use Disorder: An Overview" on page 1 for a review of medications for AUD.)*

CATR: Can you say a little bit about combination pharmacotherapy?

Dr. Petrakis: The evidence is just not good. COMBINE was the largest trial looking at this, and it found naltrexone and acamprosate together were no better than naltrexone alone. We did a study where we combined naltrexone and disulfiram in people with comorbid psychiatric illness (Petrakis IL et al, *Biol Psychiatry* 2005;57(10):1128–1137). Our great hypothesis was that naltrexone would diminish craving and disulfiram would help control impulsive drinking, and that together they would be better than each one alone. But that's not what we found at all; there was no advantage to the combination. There have been other trials, and a suggestion that combination therapy might be helpful at least early on (Anton RF et al, *Am J Psychiatry* 2011;168(7):709–717), but nothing has been really convincing that using multiple medications for the long-term treatment of AUD is the way to go. Does that mean you never try combinations? Maybe not. I would go with the evidence-based monotherapies before mixing them, though.

CATR: And what about psychotherapy for patients with comorbid AUD and mental illness?

Dr. Petrakis: There are really two questions there: psychotherapy for AUD itself, and psychotherapy for whatever the comorbid psychiatric illness might be. Let's talk about psychotherapy for AUD first. There are several interventions designed to specifically address AUD, mostly derived from a cognitive behavioral framework (Magill M et al, *Behav Res Ther* 2020;131:103648). I think these are important and can be very helpful for some patients.

CATR: And what about psychotherapy for the comorbid mental illness?

Dr. Petrakis: Psychotherapy certainly isn't contraindicated. At one time, there was concern about patients with comorbid PTSD undergoing exposure therapy or cognitive processing therapy. There was worry that the anxiety brought up in the treatment might drive patients to drink. But I don't know of any data that bear this out. In fact, there's evidence that exposure therapy might be the optimal approach for patients with comorbid PTSD and AUD (Norman SB et al, *JAMA Psychiatry* 2019;76(8):791–799).

CATR: Many practitioners have differing beliefs about the proper chronology of treatment. Should treatment focus on AUD first and then comorbid mental illness, the other way around, or both at once?

Dr. Petrakis: Well, it depends how the patient is presenting; it's a question of acuity. Clearly, for someone presenting with suicidality, safety and stabilization are the priority. Similarly, if someone is presenting in withdrawal, detox is the most pressing issue. But those are obvious examples. In general, you shouldn't wait to treat either the AUD or the other psychiatric issue. The old-fashioned approach said patients should be sober for a month before treating depression because mood gets better over time. And while it's true that mood does tend to get better over time, that approach results in a patient waiting around suffering from depression, risking dropping out of treatment, and possibly having a bad outcome.

CATR: And most of the pharmacologic approaches are quite safe even if a patient is drinking.

Dr. Petrakis: Nowadays, yes. Prescribers worried about giving medications like tricyclics, MAOIs, or lithium to heavy drinkers. But SSRIs are safe and shown to be effective in combination with naltrexone for depression (Pettinati HM et al, *Am J Psychiatry* 2010;167(6):668–675). At this point, concurrent treatment really is standard of care.

CATR: Thank you for your time, Dr. Petrakis.

AUDIT-C

How often do you have a drink containing alcohol?	
0 points: Never	3 points: 2–3 times a week
1 point: Monthly or less	4 points: 4 or more times a week
2 points: 2–4 times a month	
How many standard drinks containing alcohol do you have on a typical day?	
0 points: 1–2	3 points: 7–9
1 point: 3–4	4 points: 10 or more
2 points: 5–6	
How often do you have six or more drinks on one occasion?	
4 points: Daily or almost daily	1 point: Less than monthly
3 points: Weekly	0 points: Never
2 points: Monthly	

In men, a total score of 4 or more is positive.

In women, a total score of 3 or more is positive.

The higher the score, the more likely that a person's drinking is affecting their safety.

Source: Adapted from Bush K et al, Arch Intern Med 1998;158(16):1789–1795

Common Terms for Alcohol Drink Sizes

Term	Volume	Number of Standard Drinks of 40% Liquor
Nip/shot[1]	50 mL	1
Half-pint	200 mL	4.5
Pint	375 mL (not actually a pint, but half of a fifth)	8.5
Fifth	750 mL (size of standard wine bottle, approx. 1/5 of a gallon)	17
Handle/half-gallon	1.75 L	40

[1]Nips and shots are similar but not exactly the same. A nip usually refers to a miniature bottle that contains 50 mL, whereas a shot refers to a small glass that typically will hold 1.5 fluid ounces, which is 44 mL.

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FDA-approved meds

Naltrexone (ReVia, Vivitrol)

Naltrexone is an opioid receptor antagonist that decreases alcohol cravings by blunting the reinforcing pleasure induced by a drink. Many patients find naltrexone to be particularly user-friendly because it is usually well tolerated, can be taken as a single daily pill, and can be started while actively drinking. It is generally taken as a daily 50 mg dose, though 25–100 mg doses are also possible. While alternate dosing strategies exist, a single daily dose seems to be as effective as any other strategy and is certainly the simplest option (Jonas DE et al, *JAMA* 2014:311(18):1889–1900).

Naltrexone is also available as a 380 mg monthly injectable (Vivitrol), which is a great option when adherence is a concern, though it is important to note that we lack quality head-to-head trials to determine the comparative efficacy of oral versus injectable naltrexone. Pain at the injection site can be problematic, and at least anecdotally, the naltrexone injection is more uncomfortable than other depot medications for some patients. High cost and special storage requirements (ie, refrigeration) can be additional barriers.

Except in special circumstances, naltrexone can't be administered alongside opioids, as it can precipitate immediate withdrawal. On the other hand, the naltrexone injection is approved for treatment of opioid use disorder (OUD), so it can be utilized for patients with comorbid AUD and OUD as long as they don't have any opioids in their system at the time of administration. Naltrexone can be rough on the liver, so it is not recommended for patients with acute hepatitis or transaminases that are five times the upper limit of normal or above.

Disulfiram (Antabuse)

Disulfiram was approved by the FDA back in 1951 as an aversive therapy for AUD. It creates a buildup of acetaldehyde by inhibiting aldehyde dehydrogenase (refer to diagram below), causing very uncomfortable flushing, headache, tachycardia, nausea, and vomiting. Many patients experiencing a disulfiram reaction will present to the hospital, and mixing large amounts of alcohol with disulfiram can cause myocardial infarction and respiratory depression.

Disulfiram can be started as soon as 12 hours after the last drink with a single dose of 250–500 mg daily. After the first two weeks, doses are typically kept to a single 250 mg daily dose to minimize hepatotoxicity. Patients should abstain from alcohol for 14 days after taking disulfiram, though in reality many can drink after seven days. Disulfiram is generally well tolerated, though it can cause an odd metallic taste. Rare but serious side effects include psychosis and severe hepatotoxicity, so liver function tests (LFTs) should be monitored. Finally, some patients are very sensitive and may react to alcohol-based hand sanitizers, mouthwash, or foods cooked with alcohol. For these patients, consider lowering the dose to 125 mg daily.

Because disulfiram is purely an aversive treatment and does not decrease alcohol cravings, it can be a bit of a double-edged sword. Patients with poor impulse control may drink alcohol with disulfiram in their system and get sick enough to require hospitalization. Other patients may stop taking the medication altogether and resume drinking. In fact, disulfiram has been shown to work only for patients who have caretakers (loved ones or a visiting nurse) directly observing adherence (Jonas et al, 2014).

Acamprosate (Campral)

Acamprosate is a viable option, especially for patients who have already achieved abstinence. Its effect size is moderate, with some studies finding that it is not quite as good as naltrexone (Anton RF et al, *JAMA* 2006;295(17):2003–2017); however, it is not hepatically metabolized, making it a good choice for those with liver disease. Acamprosate's molecular structure resembles GABA, and it is thought to enhance activity of GABA-ergic systems while also blocking glutamate receptors. How this translates to decreased alcohol use is not entirely clear.

Acamprosate is dosed TID, which is a challenge for many patients. It can be started at BID dosing, but the goal is 666 mg TID since BID dosing did not achieve statistical significance over placebo in the original clinical trial. It also requires renal adjustments: Give 50% of the dose in patients with creatinine clearance (CrCl) between 30 and 50 mL/min, and avoid it altogether in patients with CrCl less than 30 mL/min.

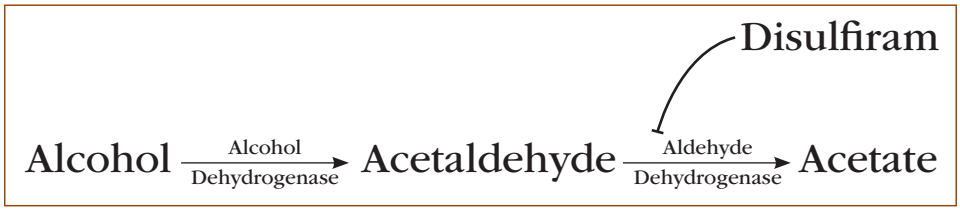
Non-FDA-approved medications

Gabapentin (Neurontin)

Gabapentin was found to be efficacious for AUD in two clinical trials (Mason BJ et al, *JAMA Intern Med* 2014;174(1):70–77; Furieri FA et al, *J Clin Psychiatry* 2007;68(11):1691–1700). The theory is that by boosting central GABA, gabapentin blunts neuronal hyperexcitability that comes from chronic drinking. It is safe for patients with liver disease but, like acamprosate, needs renal dose adjustments. Side effects include somnolence, headache, dizziness, ataxia, and peripheral edema.

Evidence shows that higher doses of gabapentin are more effective than lower doses, with one of the major gabapentin trials demonstrating clear benefit in 1800 mg versus 900 mg daily (Mason et al, 2014). Gabapentin absorption goes down as the dose goes up, known as zero-order kinetics, so the recommended target dose is 600 mg TID as opposed to the more user-friendly BID dosing. A slow titration can minimize sedation in the beginning of treatment.

Finally, be cautious in patients with comorbid OUD; gabapentin has been associated with an increased risk of



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opioid overdose death (Gomes T et al, *PLoS Med* 2017;14(10):e1002396). One trial showed that adding gabapentin to oral naltrexone improved drinking outcomes, at least over the six weeks of the trial (Anton RF et al, *Am J Psych* 2011;168(7):709–717).

Topiramate (Topamax)

Topiramate has been shown to reduce the number of heavy drinking days among patients still using alcohol (Johnson BA et al, *JAMA* 2007;298(14):1641–1651). Its mechanism of action is thought to hinge on its ability to block glutamate, which in turn reduces dopamine and dampens alcohol's reinforcing effects.

Topiramate's most notorious side effect is confusion, earning it the famous nickname "Dopamax." Other common side effects include paresthesia, loss of appetite, and itching. Rare but serious side effects include metabolic acidosis and acute closed-angle glaucoma, which can manifest early as changes in color vision. In order to mitigate side effects, titrate slowly up to 100–150 mg BID over six to eight weeks, which is the dosage that confers the greatest benefit.

Other off-label options

Varenicline (Chantix)

Varenicline is well tolerated by most patients and has demonstrated potential in AUD, especially in patients who smoke, though the data are mixed. A recent meta-analysis found that varenicline decreased cravings but not actual drinking (Gandhi KD et al, *J Clin Psychiatry* 2020;81(2):19r12924). Interestingly, it seems that varenicline might be effective for men but not women (O'Malley SS et al, *JAMA Psychiatry* 2018;75(2):129–138). At the end of the day, the evidence to recommend varenicline is not very strong, and it should be considered only after the failure of other medications with better evidence. Varenicline might have an edge over some of the other second-line medications if your patient smokes. Finally, previous concerns about adverse neuropsychiatric events were likely overblown—recent trials have reassured us that varenicline is safe to prescribe in patients with comorbid psychiatric disorders (Anthenelli RM et al, *Lancet* 2016;387(10037):2507–2520).

Baclofen (Lioresal)

Baclofen is a GABA-B agonist thought to reduce alcohol cravings and, in turn, lead to abstinence through its GABAergic actions. Despite some promising early reports, further studies have revealed heterogeneous results, with baclofen performing no better than placebo on most drinking outcomes in a large meta-analysis (Rose AK and Jones A, *Addiction* 2018;113(8):1396–1406). Given the relatively weak evidence, we recommend trying baclofen only after other medications have failed. Keep in mind that baclofen is a central nervous system (CNS) depressant associated with toxicity and misuse, so be especially cautious if the patient is heavily drinking or taking other sedating medications (Reynolds K et al, *Clin Toxicol (Phila)* 2020;58(7):763–772).

Ondansetron (Zofran)

Ondansetron, which you probably know as an antiemetic, has been shown to decrease drinking in several older trials (Sellers EM et al, *Alcohol Clin Exp Res* 1994;18(4):879–885). Its anti-drinking properties are thought to come from serotonin 5-HT3 antagonism. Interestingly, researchers have thought that people who develop AUD at a young age are more likely to have disruptions in serotonin signaling, and sure enough, ondansetron does seem to be more effective for these patients (Johnson BA et al, *JAMA* 2000;284(8):963–971). It also seems to work better for patients who do not drink very heavily—less than 10 drinks daily. Ondansetron's distinguishing side effect is QTc prolongation, so avoid it in patients who have cardiac disease or are taking other QTc-prolonging medications. Other side effects include increased LFTs, constipation, diarrhea, and headache. Though not entirely contraindicated, we would not recommend the use of ondansetron for patients on serotonergic medications since there is an increased risk of serotonin syndrome.

SSRIs

SSRIs have been examined for their efficacy in AUD. Whether they might decrease drinking by centrally modulating serotonin, or simply by treating underlying depression and anxiety, is unclear. Either way, the data are mixed. Among the SSRIs, sertraline has some of the best evidence, particularly for patients without a family history of AUD or who developed AUD later in life (Pettinati HM et al, *Alcohol Clin Exp Res* 2000;24(7):1041–1049), although fluoxetine showed efficacy in early trials and citalopram has some promising preclinical data. Nothing in this class is particularly convincing. Consider SSRIs for patients who have failed other more established treatments, especially if they have comorbid depression or anxiety.

Our decision tree

With all the medication options out there, how do you choose among them for your patients? Here's our quick decision tree:

First line

Naltrexone

- Our first choice for most patients
- Effective whether patients are drinking or not
- Can be given orally or as a long-acting injectable
- Cannot combine with opioids, but a good option for patients with comorbid OUD

Acamprosate

- Second choice after naltrexone
- Mainly indicated for patients who are already abstinent
- Good for patients with liver disease; renal dosing necessary

Second line

Gabapentin

- Effective but can be misused
- Associated with increased risk of opioid overdose

Topiramate

- Effective whether patients are drinking or not
- Cognitive and other side effects problematic

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Q&A With the Expert

Alcohol-Induced Liver Disease

Ramon Bataller, MD

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Dr. Bataller has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

CATR: Many non-specialists find the jargon of the liver field confusing. Can we start by reviewing the relevant terminology that clinicians should be familiar with?

Dr. Bataller: The best way to do that is by reviewing the natural history of alcohol-related liver disease. Most people who drink excessively accumulate fat in the liver; this is an early stage of disease called *steatosis*. This fat can develop inflammation, which is called *steatohepatitis*. Over time, steatohepatitis results in scar tissue deposition called *fibrosis*. Early on, fibrosis itself is asymptomatic and can only be seen with imaging or biopsy. *Cirrhosis* is when the fibrosis becomes extensive enough that it impairs liver function. That is the natural history of chronic liver disease *(Editor's note: See figure on page 9)*. Patients who drink heavily can develop an acute medical condition called alcoholic hepatitis, which is a rapid form of liver failure often characterized by jaundice and ascites. It is increasingly seen in young women, who are especially vulnerable to this condition, and has a mortality as high as 25% in one month and greater than 50% over five years (Hosseini N et al, *Alcohol and Alcoholism* 2009;54(4):408–416).

CATR: In other words, early detection is key.

Dr. Bataller: Absolutely. A big problem in the field is the focus on advanced disease instead of prevention or early detection. To make an analogy, it's as if the colon cancer field were only focused on metastatic disease. Of course, we know that routinely performing colonoscopies for patients older than 45 can identify early cancers and precancerous growths. We need to have the same approach in patients with excessive drinking.

CATR: What should clinicians be focusing on with their patients in the office?

Dr. Bataller: The number one thing is to identify people who drink heavily, and alcohol is so often underreported. Sometimes it's for job security or health insurance, but usually it's stigma or shame. So, a gentle non-judgmental approach is critical. First, very simply, you need to sit with your patients. You need to devote time. That goes a long way in building trust. I've found that educating patients about the genetic contribution to alcohol use disorder (AUD) can be helpful too. I ask about first-degree relatives with problematic drinking, and most patients who drink also have family members who drink. If so, I say, "This is not your fault. Your genes make you more vulnerable to alcohol problems, and this is the case with many of my patients, but we can work to solve this together." This can be helpful especially for patients who might have lost a job or personal relationships because of alcohol; there can be a lot of self-blame, and this approach can give some relief.

"For me, when it comes to treating patients for hepatitis C (HCV) who are actively drinking, it's an ethical issue. So, if your patient might benefit from HCV treatment, you should advocate for it; many people will improve if their HCV is cured. Alcohol use also increases risky sexual behavior, drug use, and needle sharing. So, treating HCV in patients who continue to drink protects the public as well."

Ramon Bataller, MD

CATR: Are there specific techniques that you find useful?

Dr. Bataller: There are two simple techniques that I learned working with addiction therapists over the years. The first is "overshooting." Rather than asking, "How many drinks do you have each day?" I'll ask, "How many drinks do you have a day—10 to 15?" In response, the patient may say, "Oh, no, I only have five." Likewise, I'll ask, "Was your last drink yesterday or a week ago?" They'll say, "No, doctor, it was two weeks ago." The other technique is asking about withdrawal symptoms. If I suspect that a patient drinks a lot, but they are not forthcoming, I'll ask, "If you stopped drinking 100% now—not a single sip—will you start shaking? Will you start sweating and vomiting?" If the patient says yes, then I know two things: 1) that patient is a heavy drinker, and 2) they need detox in order to be able to reach total abstinence.

CATR: What else should clinicians be looking for specifically related to alcohol-induced liver disease?

Dr. Bataller: A good physical exam can be very revealing. We learn all about the signs in medical school, yet we often don't look for them in actual clinical practice. Hepatomegaly, splenomegaly, and ascites are physical signs that can give you a good idea of the patient's liver status. Clinicians should examine for these. As a hepatologist, I perform thorough physical exams on all my patients, though I understand that some psychiatrists do not routinely do them outside of the emergency department or specialty clinic settings. Even so, you can pick up other important signs just through observation. A keen eye

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can pick up spider angioma, gynecomastia, and palmar erythema as long as you are looking for them. Jaundice can be seen anywhere on the skin, but pay particular attention to the inside of the eyelids.

CATR: And what about labs? Many non-experts look at alanine and aspartate transaminase (ALT and AST), maybe bilirubin, and that's it. Can you walk us through the liver function tests?

Dr. Bataller: Well, ALT and AST are important. They become elevated from direct hepatocyte injury and inflammation. Typically, ALT is more elevated in non-alcoholic fatty liver disease, and AST is higher in alcohol-related liver disease. Increased bilirubin, increased international normalized ratio (INR), and decreased albumin reflect liver failure, a more advanced stage of liver disease. Mild elevations in ALT and AST (less than five times normal) do not necessarily imply liver dysfunction, and it is not necessary to adjust doses or hold hepatically metabolized medications. Gamma-glutamyl transpeptidase (GGT) is ordered less often but is more sensitive in detecting liver damage from alcohol. You usually see levels eight or 10 times normal in patients who drink heavily. There are also hematologic abnormalities with certain patterns suggesting heavy alcohol use: low platelets and white blood cells from bone marrow toxicity, and macrocytic anemia from B12 deficiency. You can also see elevated iron; interestingly, I sometimes get consults for hemochromatosis, but it turns out the patients actually have AUD. Transferrin is an enzyme that is involved in maintaining iron balance, and carbohydrate-deficient transferrin (CDT) is elevated in patients who drink heavily. You can order this as a separate lab test, but I don't order it frequently because it doesn't provide information that the other tests don't already reveal.

CATR: What about bilirubin and alkaline phosphatase?

Dr. Bataller: Bilirubin starts as unconjugated and is a natural product of hemoglobin breakdown. It is measured as *indirect bilirubin*. This goes to the liver, where it is conjugated so that it can be excreted. That's measured as *direct bilirubin*. Typically, both are elevated in people with liver failure from alcohol. Alkaline phosphatase can be elevated for many reasons, but for our purposes, it is a marker of bile flow. Obstruction from a stone or cancer will increase the level. It's minimally elevated in alcoholic liver disease, and only gets very high when liver damage is in an advanced stage and causes the liver to become dysmorphic and inflamed.

CATR: We hear about synthetic function. What does that mean and why is it important?

Dr. Bataller: So far, the labs we've talked about measure liver damage. But equally important is how well the hepatocytes are functioning. That's what we mean when we say "synthetic function." Because unconjugated bilirubin is produced constantly by the body, and the liver actively converts it into conjugated bilirubin, both direct and indirect bilirubin measurements are indicators of the synthetic function of the liver. In fact, of all the markers of synthetic function, bilirubin has the greatest predictive value of mortality in patients with alcohol-induced liver disease (Parker R et al, *Clin Gastroenterol Hepatol* 2021;S1542-3565(21)00092-6). If a patient with elevated bilirubin is able to stop drinking, and their bilirubin level drops back to normal, that means their liver's synthetic function has returned, and that patient has a good prognosis. If a patient's bilirubin keeps increasing even during abstinence, that means the liver's synthetic function has been permanently impaired, and that results in a very poor prognosis; their mortality is more than 50% at three months.

CATR: Should we be aware of any other measures of synthetic function?

Dr. Bataller: Other measures of synthetic function are the proteins that the liver makes. One of the main ones is albumin, which makes up about half of all the circulating protein in the blood, and its production can be impaired in patients with cirrhosis. Since it is so abundant, albumin is one of the main determinants of intravascular oncotic pressure; therefore, low albumin levels can result in capillary leak and contribute to ascites accumulation. The liver also makes clotting factors, so people with impaired synthetic function have an elevated INR. Patients with advanced cirrhosis can have very high bleeding risk.

CATR: Of all these labs, which would you recommend that mental health providers order for screening purposes?

Dr. Bataller: Every patient seen with AUD or excessive alcohol intake should be checked with ALT, AST, GGT, bilirubin, an iron panel, albumin, coags, and a complete blood count. In patients with known liver disease, clinicians can estimate the degree of liver scarring using routine lab values (Moreno C et al, *J Hepatol* 2019;70(2):273–283). I recommend the FIB-4 Index, which estimates the amount of scarring in the liver using the patient's age, platelet count, and ALT/AST values. It is important to calculate the amount of scarring if you are considering starting a medication like disulfiram, which can cause liver failure in patients with advanced fibrosis. Avoid disulfiram in patients with a FIB-4 score of 5 or above, and be very cautious if the score is above 2. *(Editor's note: See "Important Laboratory Values" table on page 9.)*

CATR: What about naltrexone dosing?

Dr. Bataller: Believe it or not, there has never been a clinical trial of naltrexone in patients with alcohol-related liver disease. Naltrexone can be an effective medication, but it comes with three red flags: 1) It can cause hepatotoxicity, less so than disulfiram, but I don't recommend it for patients with liver failure; 2) At least anecdotally, it can cause encephalopathy, especially in people with cirrhosis; and 3) It can precipitate opioid withdrawal if patients have any opioids in their system. So, clinicians should be careful with naltrexone in patients with opioid use disorder (OUD). Of course, naltrexone isn't contraindicated in patients with OUD, and the injectable form is actually an approved OUD treatment, but clinicians should just be cautious.

CATR: What lab values are important to consider when prescribing naltrexone?

Dr. Bataller: Avoid naltrexone if transaminases are very high, five times the upper limit of normal. But if that is the case, there is usually more going on than just heavy drinking. More important are the synthetic markers we

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Expert Interview – Alcohol-Induced Liver Disease

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Natural History of Alcoholic Liver Disease

Steatosis

Accumulation of fat in the liver
(normal laboratory values or increased GGT)

↓

Steatohepatitis

Fatty liver with inflammation
(elevated laboratory markers of liver inflammation)

↓

Fibrosis

Formation of scar tissue from chronic inflammation
(not reflected in laboratory values early on; seen on non-invasive tests)

↓

Cirrhosis

Scarred liver with impaired function
(decreased synthetic function on laboratory values)

Important Laboratory Values	
Markers of Inflammation	
Alanine transaminase (ALT)	More elevated in non-alcoholic fatty liver
Aspartate transaminase (AST)	More elevated in alcoholic liver disease
Gamma-glutamyl transpeptidase (GGT)	Most sensitive for alcoholic liver disease
Markers of Synthetic Function	
Albumin	Decreased in alcoholic liver disease
Direct bilirubin	Increased in alcoholic liver disease
Indirect bilirubin	Increased in alcoholic liver disease & malnutrition
International normalized ratio (INR)	Increased in alcoholic liver disease
Other Relevant Labs	
Iron panel	Iron accumulates in alcoholic liver disease
Mean corpuscular volume	Elevation indicative of B12 deficiency
Platelet count	Decreased in alcoholic liver disease
White blood cell count	Decreased in alcoholic liver disease

discussed before: bilirubin, albumin, and INR. There are no studies or established protocols here, so this is an expert opinion, but I would not give naltrexone to patients with total bilirubin greater than 3 or INR greater than 1.5. That indicates synthetic dysfunction and risks further hepatotoxicity. That being said, naltrexone can be cautiously considered in these patients as long as they are monitored carefully. I've taken this risk and succeeded in a few cases.

CATR: Do you adjust the dose for these patients?

Dr. Bataller: Again, there is no evidence base, but I start with 50% of the dose in patients with impaired synthetic function. That is, if I decide to use naltrexone at all.

CATR: We've discussed disulfiram and naltrexone. What about other medications for AUD in patients with liver disease?

Dr. Bataller: Acamprosate is the only one left that is FDA approved. But there are others with varying amounts of evidence: gabapentin, baclofen, and topiramate. These all seem to be safe. For an overview, I recommend a review article I co-wrote discussing these medications in the setting of alcoholic liver disease (Arab JP et al, *Nat Rev Gastroenterol Hepatol* 2022;19(1):45–59).

CATR: How does comorbid viral hepatitis affect all this?

Dr. Bataller: Well, it makes everything worse, as you might imagine. The laboratory monitoring that we discussed is the same, whether you are talking about alcoholic liver disease or viral hepatitis. Obesity increases fat deposition in the liver as well and accelerates disease progression. Of course, research studies try to isolate causes of disease and treatments, but in real life, comorbidity is common. We may treat hepatitis C (HCV), but if the patient is still drinking heavily, their liver disease won't get any better. So, we need to treat comorbidities; we have to be holistic and inclusive.

CATR: Would you treat HCV in a patient who is actively drinking?

Dr. Bataller: That is a very good question, and different providers will answer differently. For me, it's an ethical issue, and I say yes. I always say, "You're not a judge; you're not a police officer; you're not a priest. You're a doctor." So, if your patient might benefit from HCV treatment, you should advocate for it; many people will improve if their HCV is cured. People who continue to drink heavily are likely to still have active liver disease even after treating HCV, but as physicians, we have a mission to protect public health as well. Alcohol use also increases risky sexual behavior, drug use, and needle sharing. So, treating HCV in patients who continue to drink protects the public as well.

CATR: And finally, when should mental health and addiction providers consider expert hepatology consultation?

Dr. Bataller: First of all, we should be working together much more. We work in silos, but of course the patient's organ systems are all connected and affect one another. Ideally, every addiction center should have a hepatologist linked to it. But more generally, early detection of disease and referral is best. Review the labs we talked about earlier, and consider making a referral to a hepatologist at any sign of underlying cirrhosis, liver failure as indicated by impaired synthetic function, or clinically obvious jaundice.

CATR: Thank you for your time, Dr. Bataller.

Research Updates

METHAMPHETAMINE

Add-On Buprenorphine for Methamphetamine Use Disorder

Sanya Virani, MD. Dr. Virani has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

REVIEW OF: Kheirabadi GR et al, *J Clin Psychopharmacol* 2021;41(1):45–48
STUDY TYPE: Randomized controlled trial

Methamphetamine (meth) addiction is notoriously difficult to treat. There are no FDA-approved medications, and even the most promising trials have mixed results. People withdrawing from meth experience dysphoria, anxiety, mood instability, sleep disturbances, and intense drug cravings. In this study, researchers chose to investigate whether treating drug cravings could decrease participants' meth use, and secondarily, whether this would lead to improvements in the depression, stress, and anxiety experienced during withdrawal. Targeting cravings seems intuitive, but the researchers made the unusual decision to use buprenorphine (bup), the mu-opioid partial agonist, as their anti-craving agent.

Bup is best known as a treatment for opioid use disorder (OUD), but it is hypothesized to have the potential for more general anti-craving effects by inducing dopamine release from the nucleus accumbens. While we don't have any convincing human data yet, animal studies have shown that bup alters the dopamine neurotransmission brought about by meth that is thought to correlate with drug craving (Pereira FC et al, *Neurotox Res* 2011;19(1):94–101). The researchers in this study therefore theorized that bup's potential anti-craving effect might be applicable to patients addicted to meth.

The researchers conducted a randomized, double-blind, placebo-controlled trial of 40 participants (30 men and 10 women), with an average age of 32.3 years and an average meth-addiction duration of 2.49 years. Half were assigned to receive bup (2 mg daily for one week, 4 mg daily for six weeks, then 2 mg for one week) while half received placebo. All participants enrolled in the same 16-week intensive multimodal psychotherapy program.

Over the study's 24 weeks, those taking bup did better on all outcomes. Drug cravings were measured weekly for the first eight weeks and monthly thereafter, and the intervention group had modestly but significantly lower drug cravings at all time points after the first two weeks. Consistent with the hypothesis that treating cravings might improve sobriety, the intervention group had fewer meth-positive urine tests, with a mean of 5.80 positives in the bup group versus 7.80 in the placebo group ($p < 0.001$). Secondary endpoints of depression, anxiety, and stress were also slightly better in the treatment group versus the placebo group, at least at the two-month time point, which was the only time point reported in the study.

The small number of trial participants is a limitation, but not unusual for a study of this nature. However, several other key questions are left unanswered. Whether participants had a period of sobriety at the time of enrolling in the trial was not addressed. Neither was the authors' choice to use unusually tiny doses of bup. And while outcomes reached statistical significance, the clinical utility of this approach remains questionable.

CATR'S TAKE

Bup did reduce cravings and abstinence in people with meth addiction in this small study, but lots of question marks remain about prescribing an unusual dose of a controlled substance for a non-FDA-approved indication. This approach is promising, so keep an eye out for future developments, but prescribing bup for meth addiction should remain in the realm of research until we have better clinical data. In the meantime, see the May/June 2021 *CATR* for a Q&A and clinical update on treating stimulant use disorders.

OUD

Unintended Pregnancies in Opioid Use Disorder

Peter J. Farago, MD. Dr. Farago has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

REVIEW OF: Heil SH et al, *JAMA Psychiatry* 2021;78(10):1071–1078
STUDY TYPE: Randomized controlled trial

Among women with opioid use disorder, nearly eight out of every 10 pregnancies are unintended (Fischbein RL et al, *Contracept Reprod Med* 2018;3:4). The complications and potential adverse outcomes of these pregnancies include neonatal opioid withdrawal syndrome (NOWS), microcephaly, and miscarriage, with many newborns suffering future developmental delay and disability. The economic impact is profound, costing Medicaid an estimated $600 million annually in additional healthcare expenses for NOWS-related postnatal care alone.

This new study, funded by the National Institutes of Health, examined the efficacy and cost benefit of co-locating contraceptive services and addiction treatment for patients with OUD. Over a three-year period, researchers enrolled 138 women who were receiving medication for OUD and were at high risk for unintended pregnancy. Participants had a mean age of 30.6 years (range 20–44), and 92% were white. Participants were randomized to receive one of three interventions: usual care (education and referral to community health care facilities); on-site contraceptive services (located in the same building as substance use treatment) plus six months of follow-up visits; or the same on-site contraceptive services plus financial incentives for attending follow-up visits. Each participant was followed for one year, and the primary outcome was verified contraceptive use at six-month follow-up. Secondary outcomes included contraceptive use at 12 months, use of a long-acting contraceptive such as an intrauterine device or an implant, and unintended pregnancy.

The analysis showed that co-located contraceptive and addiction services outperformed usual care, and that the group

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CE/CME Post-Test

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These questions are intended as a study guide. Please complete the test online at www.carlataddictiontreatment.com. Learning objectives are listed on page 1.

1. Which medication for alcohol use disorder (AUD) should be considered first line for a patient with comorbid opioid use disorder and history of poor medication adherence (LO #1)?
   [ ] a. Gabapentin [ ] b. Acamprosate [ ] c. Topiramate [ ] d. Injectable naltrexone
2. According to Dr. Bataller, which of the following lab values is the most specific for alcoholic liver disease (LO #2)?
   [ ] a. Elevated alanine transaminase (ALT) [ ] c. Elevated aspartate transaminase (AST)
   [ ] b. Decreased direct bilirubin [ ] d. Elevated albumin
3. According to a 2021 study of methamphetamine (meth) use disorder, participants randomized to buprenorphine (bup) started to have significantly lower drug cravings compared to the control group after how many weeks of treatment (LO #3)?
   [ ] a. Two weeks [ ] b. Four weeks [ ] c. Eight weeks [ ] d. 12 weeks
4. In patients who have achieved abstinence, acamprosate has a moderate effect size for AUD, and it can be used in patients with liver disease (LO #1).
   [ ] a. True [ ] b. False
5. Which co-occurring psychiatric disorder has the highest prevalence with AUD (LO #2)?
   [ ] a. Anxiety disorders [ ] c. Bipolar disorder
   [ ] b. Major depressive disorder [ ] d. Posttraumatic stress disorder
6. In a 2021 study, what was concluded about the efficacy of bup for meth use disorder, compared to placebo (LO #3)?
   [ ] a. Bup improved stress but had no effect on anxiety or depression at two-month follow-up
   [ ] b. There was no significant difference in number of meth-positive urine tests between the bup and placebo groups
   [ ] c. Bup did not improve depression, anxiety, or stress at any time point in the study
   [ ] d. The bup group had significantly fewer meth-positive urine tests
7. In a 2017 study of patients with AUD who were still drinking, which medication reduced the number of heavy drinking days (LO #1)?
   [ ] a. Baclofen [ ] b. Topiramate [ ] c. SSRIs [ ] d. Varenicline
8. According to Dr. Bataller, which synthetic marker has the greatest predictive value of mortality in patients with alcohol-induced liver disease (LO #2)?
   [ ] a. Albumin [ ] c. International normalized ratio (INR)
   [ ] b. Bilirubin [ ] d. AST

Medications for Alcohol Use Disorder: An Overview

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Third line

Baclofen
- Caution in patients using other CNS depressants
- Like gabapentin, probably effective but can be misused

Disulfiram
- Only for patients who are abstinent and highly motivated
- Observed administration is helpful—in fact, it might be necessary
- Monitor LFTs periodically

Ondansetron
- Most evidence in early-onset AUD
- Can prolong QTc, so avoid in cardiac disease

SSRIs
- Low efficacy as a monotherapy
- Especially useful for patients with comorbid depression or anxiety

Varenicline
- Especially useful for patients who smoke

CATR VERDICT: We recommend naltrexone and acamprosate as first-line treatments, gabapentin and topiramate as second line, and all the rest as third line. Choose meds based on patient characteristics and side effect profile. For example, favor acamprosate and gabapentin for patients with liver disease, favor injectable naltrexone for those with adherence issues or comorbid OUD, and avoid disulfiram for patients with poor impulse control.

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Research Updates

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receiving financial incentives did the best. Verified contraceptive use was highest in the combined services with financial incentives group (40.5%), second highest in the non-incentivized combined services group (25%), and lowest in the usual care group (6.3%). Following on logically, the rate of unintended pregnancies was lowest in the incentivized group (4.9%), higher in the non-incentivized group (16.7%), and highest in usual care (22.2%). A cost-benefit analysis showed that the incentivized intervention was the most cost effective as well, with $6.96 saved for every dollar spent.

The authors point out that the study's skewed demographics, small sample size, and high intensity of intervention could limit its generalizability. They also acknowledge the debate about tying financial incentives to contraceptive services and that this could potentially be seen as coercive, especially given the history of reproductive injustice among marginalized groups.

CATR'S TAKE

Combining contraceptive care and addiction treatment decreased rates of unintended pregnancy and saved health care dollars, showing the potential benefits of co-located health care services. Though still a relatively new care model, refer your OUD patents at risk of unintentional pregnancy to such clinics if they are available in your area. If your patients wish to become pregnant, be sure to make a referral to an obstetrician.

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